isolated from liquid cultures of *Penicillium cyclopium*, *Aspergillis flavus* and *Aspergillis versicolor* (Luk *et al.*, Applied and Environmental Microbiology 211-212 (1977)). DBHQ is a commercially available non-toxic synthetic compound chemically unrelated to either thapsigargin or CPA.

Using the CF-derived pancreatic epithelial line CFPAC-1, Chao *et al.*, supra, found that DBHQ stimulated ^{125}I efflux and mobilized intracellular free Ca^{+2} in a dose-dependent manner. Pretreatment of monolayers of CFPAC-1 cells with DBHQ for 4-5 minutes significantly increased the Ca^{+2}-independent or autonomous activity of Ca^{+2}/calmodulin-dependent protein kinase (CaMKII) assayed in cell homogenates.

D. Opening the ER Ca^{+2} Channels.

Activators which lower ER Ca^{+2} by a different mechanism than thapsigargin are also encompassed by this invention.

1D-myo-inositol 1,3,4-(or 1,4,5-) triphosphate (IP_3), a hydrophilic inositol phosphate, induces the intracellular release of Ca^{+2} stores from the ER through its specific interactions with the IP_3 receptor (*e.g.*, a calcium channel protein containing an IP_3 binding site). Thus, the present invention also encompasses agents that open ER Ca^{+2} channels by acting as IP_3 receptor agonists. Adenophostin A is one example of an activator of IP_3 receptor activity (Adkins CE, Wissing F, Potter BV, Taylor CW, Rapid activation and partial inactivation of inositol trisphosphate receptors by adenophostin A, *Biochem J.*, 352 (3): 929-33, 2000).

A determination of IP_3 concentration in cell extracts can be carried out by means of a sensitive competitive binding test using an IP_3 binding protein, H^3 -labeled IP_3 and unlabeled IP_3 (U.S. Patent No. 5,942,493). An assay kit for this purpose is available from Amersham (TRK 1000) and the determination can be carried out as described in the assay protocol.

Another calcium channel found in the ER is known as the ryanodine receptor (RyR). Mammalian tissues express three different RyR isoforms comprising four 560 kD (RyR polypeptide) and four 12 kD (FK506 binding protein) subunits (reviewed in Shoshan-Barmatz, V. and Ashley, R.H., The structure, function, and cellular regulation of ryanodine-sensitive Ca^{2+} release channels, *Int Rev Cytol*, 183: 185-270, 1998.) Ryanodine receptors have been detected in the lung (Wild, J.S., Giri, S.N., Moore, R., and Pessah, Characterization of [^{3}H]ryanodine binding sites in mammalian lung, *Arch. Biochem Biophys.*, 379(1):109-18, 2000). According to the present invention, treatments that activate or stimulate ryanodine receptors may be effective in reducing ER Ca^{2+}

concentration in airway epithelial cells. Thus, the present invention also encompasses agents that increase or stimulate ryanodine receptors, thereby increasing Ca^{2+} exit from the ER. Such agents include, for example, ryanodine receptor agonists, compounds that increase expression of ryanodine receptors, etc. Approaches to modulation of ryanodine receptors are discussed in Xu, L., et al., Potential for pharmacology of ryanodine receptor/calcium release channels, *Ann NY Acad Sci*, 853: 130-48, 1998. Examples of agents that have been shown to increase or stimulate ryanodine receptor activity include, but are not limited to, ryanodine (in particular concentrations known in the art) and related plant alkaloids, xanthines, 4-Chloro-m-cresol, suramin, and ditalis glycosides. Such agents, and derivatives thereof (e.g., pharmaceutically acceptable derivatives), may be used in the practice of the invention.

E. Temperature-Dependent Delivery of the Mutant CFTR to the Plasma Membrane.

Experiments with 3T3 fibroblast cells and C127 cells grown at lower temperatures for a period of time have shown a shift in the glycosylation pattern of ΔF508 CFTR towards a more mature CFTR protein. Normal CFTR protein appears to be unaffected by the lower temperature. It has been hypothesized that at reduced temperatures there is an increased flux of the mutant protein through the Golgi complex. Thus, it has been suggested that exposing a patient's lung epithelia to a temperature below normal body temperature for a period of time might mobilize mutant CFTR to the plasma membrane of the lung epithelial cells, where the mutant CFTR can mediate chloride transport (U.S. Patent No. 5,674,898). One hypothetical method involves implanting in the patient's lung a non-toxic, non-immunogenic agent which lowers the temperature in the vicinity of the lung so that it is below normal body temperature.

F. Purinergic Receptors and Cl^- Secretion

Purinergic receptors play an important role in regulating Cl^- secretion in epithelial cells. Inoue et al. (Am. J. Physiol. Cell Physiol. 272(6):41-46 (1997)) assayed the human intestinal epithelial cell line, Caco-2, for Cl^- secretion by measuring the short-circuit current. The researchers found that responses to purinergic receptor agonists were inhibited by pretreatment with 1,2-bis(2-aminophenoxy)ethane-N,N,N',N'-tetraacetic acid-acetoxymethyl ester, thapsigargin or quinine.

G. CF and UDP-Glucose:Glycoprotein Glycosyl Transferase

As discussed above, the primary lesion in cystic fibrosis is associated with mutations in the gene encoding the CFTR which prevent it from functioning as a chloride channel at the apical surfaces of airway epithelial cells. The most common mutation (ΔF508), which occurs in 67.2% of cystic fibrosis patients, results in the synthesis of a CFTR protein which is unable to fold correctly and assume its appropriate tertiary conformation. Consequently, the protein is retained in the ER by the ER's "quality control" machinery. Several other CFTR mutations also result in mis-folding and ER retention.

Both nascent α-antitrypsin and nascent CFTR form transient associations with calnexin (also designated as p88 or IP90), a calcium-binding protein of the ER membrane. Since calnexin functions as a molecular chaperone for glycoproteins and interacts with monoglucosylated oligosaccharides, reglucosylation may function to initiate assembly between unfolded glycoproteins and the molecular chaperone (Hammond *et al.*, Proc. Natl. Acad. Sci. U.S.A. 91:913-917 (1994)).

The UGGT Protein and Gene. UGGT was found to have an apparent monomeric M_r of 150 kDa following isolation and purification from rat liver microsomes (Trombetta *et al.*, J. Biol. Chem. 267:9236-9240 (1992)). The soluble, 170 kDa UGGT isolated from *Drosophila* has an amino acid sequence of 1548 amino acids beginning with a signal peptide and terminating in a potential ER retrieval signal, HGEL (C.G. Parker *et al.*, EMBO J. 14(7):1294-1303 (1995)). The amino acid sequence was found to lack any putative transmembrane domains. The gene coding for UGGT, designated as *gpt1*, has also been identified in *Schizosaccharomyces pombe* (Fernandez *et al.*, EMBO J. 15(4):705-13 (1996)). This gene codes for a polypeptide having a signal peptide of 18 amino acids followed by 1429 amino acids with no transmembrane domain and a C-terminal tetrapeptide designated PDEL.

Functional Role of UGGT. UGGT adds glucose from UDP-glucose to high mannose glycoproteins in the presence of Ca^{2+} ions and the resulting glucosylated oligosaccharide has the same structure as the processed intermediate, $Glc_1Man_9GlcNAc_2$ (Trombetta *et al.*, Biochemistry 28:8108-8116 (1989)). Unfolded, denatured glycoproteins are substantially better substrates for glycosylation by the enzyme than are the corresponding native proteins.

Proteins that fail to fold properly are retained in the ER (or in an ER-Golgi intermediate compartment), where they are proteolytically degraded. UGGT is proposed to